

EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Of : TANG et al.
Patent No. : 6,528,784
Issued : March 4, 2003
Title : MASS SPECTROMETER SYSTEM INCLUDING A
DOUBLE ION GUIDE INTERFACE AND METHOD OF
OPERATION
Application Serial No. : 09/715,815
Reissue Application No. : 11/073394
Filed : November 16, 2000
Requestor : Applera Corporation

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**REQUEST FOR *EX PARTE* REEXAMINATION OF
U.S. PATENT NO. 6,527,784 PURSUANT TO 37 C.F.R. § 1.510**

Requester, Applera Corporation ("Applera"), hereby requests reexamination of claims 1 through 9 of U.S. Patent No. 6,528,784 ("the '784 patent") pursuant to the provisions of 37 C.F.R. § 1.510.

The '784 patent issued from Application No. 09/715,815 ("the '815 application") filed on November 16, 2000. The '815 application is a continuation-in-part of Application No. 09/454,273 ("the '273 parent application"), filed on December 3, 1999 and now abandoned. According to a Certificate of Correction appended to the '784 patent, the '784 patent has been assigned to Thermo Finnigan LLC ("Thermo").

Pursuant to the provisions of 37 C.F.R. §1.510(b), this request for *ex parte* reexamination of the '784 patent is accompanied by or includes:

1. A statement pointing out each substantial new question of patentability based on prior patents and printed publications.
2. An identification of every claim for which reexamination is requested, and a detailed explanation of the pertinency and manner of applying the cited prior art to every claim for which reexamination is requested.
3. A copy of every patent or printed publication relied upon or referred to accompanied by an English language translation of all the necessary and pertinent parts of any non-English language patent or printed publication.
4. A copy of the entire patent including the front face, drawings, and specification/claims (in double column format) for which reexamination is requested, and a copy of any disclaimer, certificate of correction, or reexamination certificate issued in the patent.
5. A certification that a copy of the request has been served in its entirety on the patent owner at the address as provided for in 37 C.F.R. §1.33(c), with the name and address of the party served indicated.

This request for *ex parte* reexamination is also accompanied by a form PTO-1645 Request for *Ex Parte* Reexamination Transmittal, a form PTO-1449 Information Disclosure Statement listing the prior art cited in this request for reexamination, a copy of the '273 parent application, a copy of the '815 application and file wrapper, and copies of the prior art considered during earlier prosecution of the '784 patent.

On February 23, 2005, Thermo filed a lawsuit in the United States District Court for the

District of Delaware against Applera, MDS, Inc. and Applied Biosystems/MDS Sciex Instruments alleging infringement of the '784 patent. Thermo asserts that "at least claim 4" of the '784 patent is infringed by the API 5000 mass spectrometer manufactured and sold by the defendants. In addition to asserting that the API 5000 does not infringe, the defendants contend that each claim of the '784 patent is invalid.

Also, on March 4, 2005, Reissue Application Serial No. 11/073394 was filed for the reissue of the '784 patent. The reissue proceeding was published in the Official Gazette on May 31, 2005.

Substantial new questions of patentability are introduced by the cited references, as indicated in the claim charts and analysis set forth below. Reexamination is requested based on the following cited references, claims charts, and analysis.

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I. THE INVENTION DESCRIBED IN THE SPECIFICATION OF THE '784 PATENT

The '784 patent is entitled "Mass Spectrometer System Including A Double Ion Guide Interface And Method Of Operation." Figure 1 depicts a preferred embodiment of the claimed mass spectrometer:

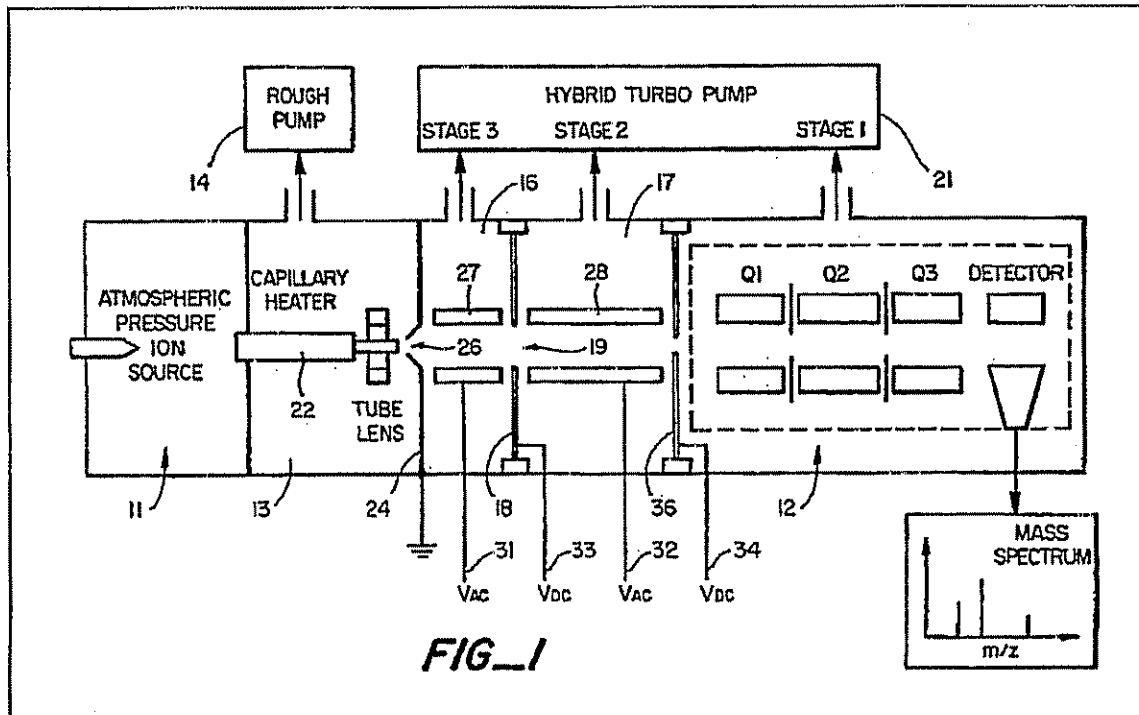


Figure 1 shows a mass spectrometer having an atmospheric pressure ion source in an atmospheric pressure chamber 11 followed by four vacuum chambers 13, 16, 17 and 12, respectively. Vacuum chambers 16 and 17 each include a RF-only quadrupole ion guide. A conical skimmer 24 separates vacuum chamber 16 from vacuum chamber 13. An interchamber lens 18 separates vacuum chamber 16 from vacuum chamber 17. A lens 36 separates vacuum chamber 17 from the mass analyzer chamber 12 which, in the case of Figure 1, houses a tandem quadrupole mass spectrometer.

The '784 patent specifies the ranges of pressures used in the two ion guide chambers: "As will be explained in accordance with the present invention, the pressure in chamber 16 is below 500 mTorr . . . and the pressure in chamber 17 is below 1 mTorr. '784, col. 4:45-50.

The '784 patent identifies the problem to which the invention is directed:

As discussed above, solvent adduct ions are formed in the high pressure regions ranging from the atmospheric pressure region to the quadrupole ion guide stages or regions. . . . The formation of adduct ions can significantly reduce the abundance of sample analyte ions which reach the analyzer. Consequently, effective conversion of the adduct ions can greatly enhance the sample ion current and the sensitivity of the mass spectrometer.

'784, col. 5:11-19. The inventors purport to have discovered "that the solvent adduct can be dissociated and converted into sample ions in the second ion guide 28 by applying a small DC offset voltage between the ion guide 28 and the lens 18 to increase the energy of the solvent adduct ions." '784, col. 5:20-24. As explained in the patent, solvent adduct ions are converted into sample ions in the second ion guide by controlling the kinetic energy of the ions such that they have enough kinetic energy in the second ion guide to dissociate the solvent molecules through collisions with neutral gas molecules in the second ion guide:

A DC voltage source is connected to provide a potential difference between the first lens and the first multipole ion guide or between interchamber lens and the second multipole ion guide or both which defines the ion's translational kinetic energy as it enters the second multipole ion guide. The ion's translational kinetic energy is chosen such that at the vacuum pressure of the second interface chamber adduct ions are converted into sample ions by collision induced dissociation without fragmentation of sample ions

'784, col. 3:27-38.

The Examiner's stated reason for allowing the pending patent claims over the cited prior art during the original prosecution of the '784 patent is set forth in the Notice of Allowability dated September 4, 2002. The Examiner stated that the cited prior art failed to teach or clearly suggest a mass spectrometer "in which sample ions and solvent molecules form adduct ions with

a reduction of sample ion current as disclosed in claims 1 and 9.” File History at Tab 18 of the Appendix to this Request, paper no. 9, pg. 3. With regard to the remaining independent claims 3 and 4, the Examiner provided much the same reason for allowance. Namely, the cited prior art failed to teach or clearly suggest a method of mass analysis wherein “some sample ions and solvent molecules combine to form adduct ion [sic] with a reduction of sample ions. . . .” *Id.*

II. SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY – ALL CLAIMS ARE UNPATENTABLE OVER PRIOR ART

Substantial new questions of patentability of claims 1 through 9 of the '784 patent under 35 U.S.C. § 102 and/or 35 U.S.C. § 103 are raised by the following prior art references. Pursuant to 37 C.F.R. § 1.510 (b)(3), a copy of each reference as well as a listing of the references on Form PTO-1449 accompanies this Request at Tab 3 of the Appendix.

- | | |
|------------------|---|
| Lazar | J. M. LAZAR et al., “Design of a Time-of-Flight Mass Spectrometer as a Detector for Capillary Electrophoresis,” <i>Analytical Chemistry</i> , 1997, vol. 69, no. 16, pp. 3205-3211. |
| Smith | R. D. SMITH et al., “Collisional Activation and Collision-Activated Dissociation of Large Multiply Charged Polypeptides and Proteins Produced by Electrospray Ionization,” <i>J. Am. Soc. Mass Spectrom.</i> , 1990, vol. 1, pp. 53-65. |
| Hager | U.S. Patent No. 6,015,972 (J. W. Hager). |
| Buchanan | M. V. BUCHANAN et al., “Continuous Octapole Electrospray Introduction System for FTICR,” 46 th <i>ASMS Conference on Mass Spectrometry and Allied Topics</i> , May 31- June 4, 1998, p. 518. |
| Thomson | B. THOMSON, “Protein Charge Distribution Studies – From Droplet in Air to Ion in Vacuum,” 44 th <i>ASMS Conference on Mass Spectrometry and Allied Topics</i> , May 12-16, 1996, p. 1092. |
| Kambara | H. KAMBARA et al., “Collision-Induced Dissociation of Water Cluster Ions at High Pressure,” <i>Int’l J. Mass Spectrom. and Ion Physics</i> , 1977, vol. 25, pp. 129-136. |
| Chowdhury | U.S. Patent No. 4,977,320 (S. K. Chowdhury et al.) |

Klientop B. L. KLEINTOP et al., "Analyzing Thermally Labile Compounds in Electrospray Sources Using Heated Capillaries," *43rd ASMS Conference on Mass Spectrometry and Allied Topics*, May 21-26, 1995, p. 905.

Kato U.S. Patent No. 5,298,743 (Y. Kato)

Tomany U.S. Patent No. 5,304,798 (M. J. Tomany et al.).

The following references are useful in so far as they provide a background for the technology at issue and the discussion of the references being relied.

Beu S. C. BEU et al., "Fourier-Transform Electrospray Instrumentation for Tandem High-Resolution Mass Spectrometry of Large Molecules," *J. Am. Soc. Mass Spectrom.*, 1993, vol. 4, pp. 557-565.

Jarvis S. A. JARVIS et al., "A New Atmospheric Pressure Ionization Orthogonal Acceleration Time of Flight Mass Spectrometer," *45th ASMS Conference on Mass Spectrometry and Allied Topics*, June 1-5, 1997, p. 1193.

Cole A. P. BRUINS, "ESI Source Design and Dynamic Range Considerations," in *Electrospray Ionization Mass Spectrometry – Fundamentals, Instrumentation, and Applications*, (R. B. COLE ed., John Wiley & Sons, Inc., 1997), chp. 3, pp. 107-136.

A. Introductory Statement Setting Forth Substantial New Questions Of Patentability

The following statement is submitted pursuant to 37 C.F.R. § 1.510(b)(1). This Request for Reexamination of the '784 patent is based upon the foregoing references and presents the following substantial new questions of patentability based upon these references.¹ As set forth in detail below, the forgoing references would have been considered important by a reasonable Examiner in deciding whether to allow the claims, particularly in view of the Examiner's stated reasons for allowance, and therefore these references raise a substantial new question of

¹ With the exception of the Hagar '972 patent, none of the prior art references relied upon in this request were of record in the prosecution of the '784 patent.

patentability. M.P.E.P. § 2242 (Rev. 2, May 2004) at 2200-48.

1. Claims 1 and 2 are unpatentable under 35 U.S.C. § 103 as obvious over either Lazar in view of Smith or Hagar in view of Lazar. Neither Lazar nor Smith were cited during the prosecution of the '784 patent and, therefore, the invalidating combinations relied upon in this request for reexamination were not available to the Examiner during the prosecution of the '784 patent. These specific combinations of references provide teachings and disclosures that were not presented during the prosecution of the '784 patent. The additional teachings and disclosures of these references include subject matter closer to the subject matter of the claims than the prior art cited during the prosecution of the '784 patent. Moreover, each combination of references provides teachings and disclosures that show the existence in the prior art of the very subject matter that formed the basis for the Examiner's allowance of the claims. Further, because claims 1 and 2 are not patentable over these prior art documents, a substantial new question of patentability is raised.²

2. Claim 3 is unpatentable under 35 U.S.C. § 102 as anticipated by any one of Smith, Kambara, Chowdhury, Kato, Klientop, Thomson, Tomany, or Hager. Neither Smith, Kambara, Chowdhury, Kato, Klientop, Thomson, or Tomany were cited during the prosecution of the '784 patent and, therefore, their teachings and disclosures were not available to the Examiner at that time. These references provide teachings and disclosures that show the existence in the prior art of the very the subject matter that formed the basis for the Examiner's allowance of the claims in the original prosecution. With respect to Hager, while Hager was cited during the prosecution of the '784 patent, this request presents Hager in a new light and in a

² A substantial new question of patentability need only be established as to one claim to support an order for reexamination for all claims. M.P.E.P. § 2216 (Rev. 2, May 2004) at 2200-26.

different manner than that applied by the Examiner during prosecution. For example, this request sets forth that Hagar expressly discloses the subject matter that formed the basis for the Examiner's allowance of claim 3. Further, because claim 3 is not patentable over each of these prior art references, a substantial new question of patentability is raised.

3. Claims 4-8 are unpatentable under 35 U.S.C. § 103 as obvious over either Lazar in view Smith, Hagar in view of Lazar, or Buchanan in view of Smith or Thomson. Lazar, Smith, Buchanan, or Thomson were not cited during the prosecution of the '784 patent and, therefore, the invalidating combinations being relied on were not available to the Examiner during the prosecution of the '784 patent. These specific combinations of references provide teachings and disclosures that were not presented during the prosecution of the '784 patent. The additional teachings and disclosures of these references include subject matter closer to the subject matter of the claims than the prior art cited during the prosecution of the '784 patent. Moreover, each combination of references provides teachings and disclosures that show the existence in the prior art of the very subject matter that formed the basis for the Examiner's allowance of the claims. Further, because claims 4-8 are not patentable over these prior art documents, a substantial new question of patentability is raised.

4. Claim 9 is unpatentable under 35 U.S.C. § 102 as anticipated by Hagar and/or under 35 U.S.C. § 103 as obvious over either Lazar in view Smith or Buchanan in view of Smith or Thomson. Lazar, Smith, Buchanan or Thomson were not cited during the prosecution of the '784 patent and, therefore, the invalidating combinations being relied on were not available during the prosecution of the '784 patent. These specific combinations of references provide teachings and disclosures that were not presented during the prosecution of the '784 patent. The additional teachings and disclosures of these references include subject matter closer to the

subject matter of the claim than the prior art cited during the prosecution of the '784 patent. Moreover, each combination of references provides teachings and disclosures that show the existence in the prior art of the very subject matter that formed the basis for the Examiner's allowance of the claim. Further, because claim 9 is not patentable over these prior art references, a substantial new question of patentability is raised.

B. Detailed Explanation of the Pertinency of Cited Prior Art References

The following discussion, and the element-by-element analysis and further discussion in part C, will serve as Applera's detailed explanation of the pertinence of each prior art reference on which Applera relies in this Request. Applera also includes in the discussion references that are indicative of the state of the art and the level of skill of the person of ordinary skill in the art as of 1999.

The '784 patent relates generally to mass spectrometers employing atmospheric pressure ion ("API") sources such as electrospray ("ESI") or atmospheric pressure chemical ionization ("APCI") sources. '784, col. 1:11-14. It was well-known prior to December 1999 (the earliest possible effective filing date of claims of the '784 patent³) that in mass spectrometer systems using API sources, and in ESI sources in particular, solvent adduct ions -- sometimes called adducts, cluster ions or clusters -- are formed. For example, a 1997 text edited by Cole explains that the problem exists and must be addressed in any API mass spectrometer:

³ In fact, with the exception of claim 3, none of the claims in the '784 patent are entitled to the December 3, 1999 filing date of the parent application. For example, the parent '273 application (at Tab 17 of the Appendix) contains no disclosure of conversion of adduct ions to sample ions in the second ion guide chamber by any other method than applying a voltage between the interchamber lens and the second ion guide. Therefore, claims that encompass the purported conversion of adduct ions to sample ions in the second ion guide chamber by adding to or defining the translational kinetic energy of adduct ions upstream of the second ion guide chamber (i.e., in the first ion guide chamber) are entitled to only the November 16, 2000 filing date of the '815 application.

In *any* design of an API mass spectrometer, the problem of the formation of cluster ions is addressed. Polar molecules that tend to cluster with ions are water and solvent vapor present in air or generated by the evaporation of the eluate from a liquid chromatograph or electrophoresis instrument connected to the API source. *All* practical designs of API instruments are aimed at either prevention of clustering, or curing the problem by breaking the clusters.

A. P. Bruins, "Chapter 3: ESI Source design and Dynamic Range Considerations," in R. B. Cole, *Electrospray Ionization Mass Spectrometry*, 1997 at 120 (emphasis added) ("Cole").

Thus, the inventors named on the '784 patent did not discover the problem of solvent adduct formation in API mass spectrometers. Nor did they discover the technique for conversion of solvent adduct ions to sample ions that is implemented in the mass spectrometer system described in the '784 patent. That technique – collisional dissociation by using an electric field to accelerate the adduct ions and collide them with neutral gas molecules – was well-known as of 1999.

1. The Conversion of Solvent Adduct Ions by Collisional Dissociation by Applying a DC Offset Voltage Between Two Electrodes Along the Ion Path Was Known Well Before 1999

In 1977, Kambara reported the results of an investigation of techniques for dissociating adduct ions in a mass spectrometer having an API source, specifically an ESI source. Kambara's instrument is depicted schematically in Figure 1 of his paper, reproduced below:

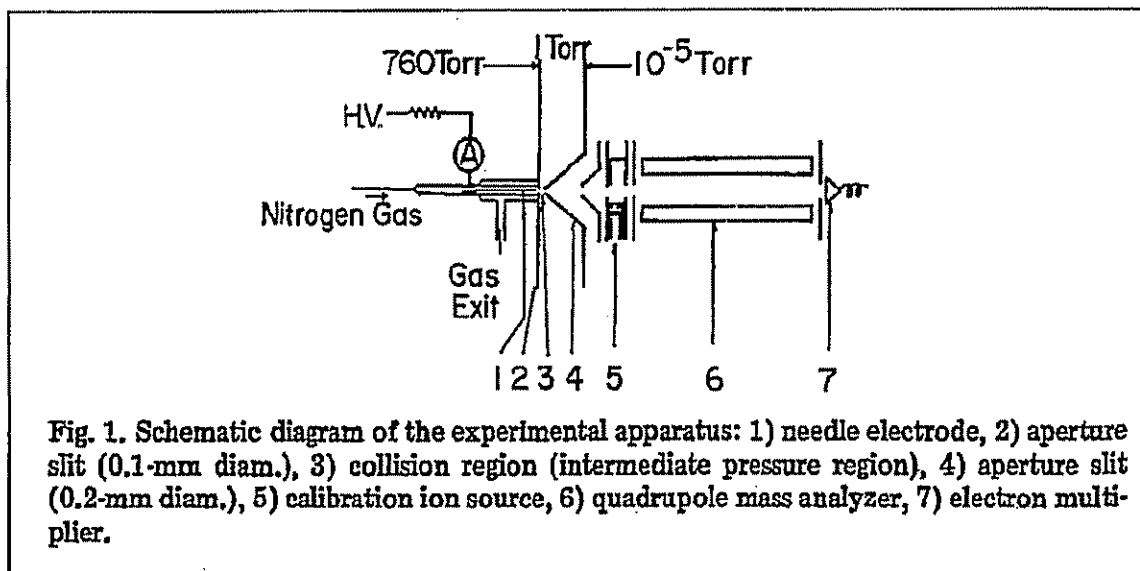


Figure 1 depicts an API source, followed by an intermediate chamber in which the pressure is approximately 1 Torr. Kambara calls the area (3) between the aperture slit (2) and the skimmer (4) in the walls that bound this intermediate chamber the "collision region." Kambara at 130. Each of the two walls is employed as an electrode through the application of voltages. *Id.* at 130-131. Kambara explains that the electric field between the two electrodes provides the ions with kinetic energy:

The electrical potential of the second aperture electrode determines the ion acceleration energy which was fixed at 3V. The electrical field strength in the intermediate [collision] region was varied by changing the electric potential of the first aperture electrode between 3 and 31 V.

Id. at 131-132.

Kambara further explains that the additional kinetic energy provided by the electric field produces collisions that dissociate cluster ions:

the cluster ions are accelerated by the electric field in the intermediate region and collide with nitrogen molecules converting part of their kinetic energy into internal energy. Finally, the excited cluster ions attain enough internal energy to dissociate into simpler ions under a sufficiently large electric field.

Id. at 131. Kambara concludes that:

[w]hether dissociation is caused by a single or multiple collision process depends on the collision energy of the cluster ions and the neutral molecules. The collision energy is determined by the electric field strength and the cluster mean free path. Assuming the cluster ions are in their ground energy states, the collision energy must be above the dissociation energy level for cluster ions to dissociate through a single collision.

Id. at 134.

Kambara, therefore, teaches the fundamental mechanism of collisional dissociation of solvent adduct ions and the relationship between each of the variables that impact that process. Simply put, an electric field produced by a DC offset voltage between electrodes along the ion path will accelerate adduct ions and dissociate them through collisions with neutral gas molecules. The magnitude of the offset voltage needed to dissociate the adduct ions will depend on, among other factors, the mean free path of the adduct ions between collisions, which is determined by the pressure in the collision region. *Id.* at footnote, p. 132.

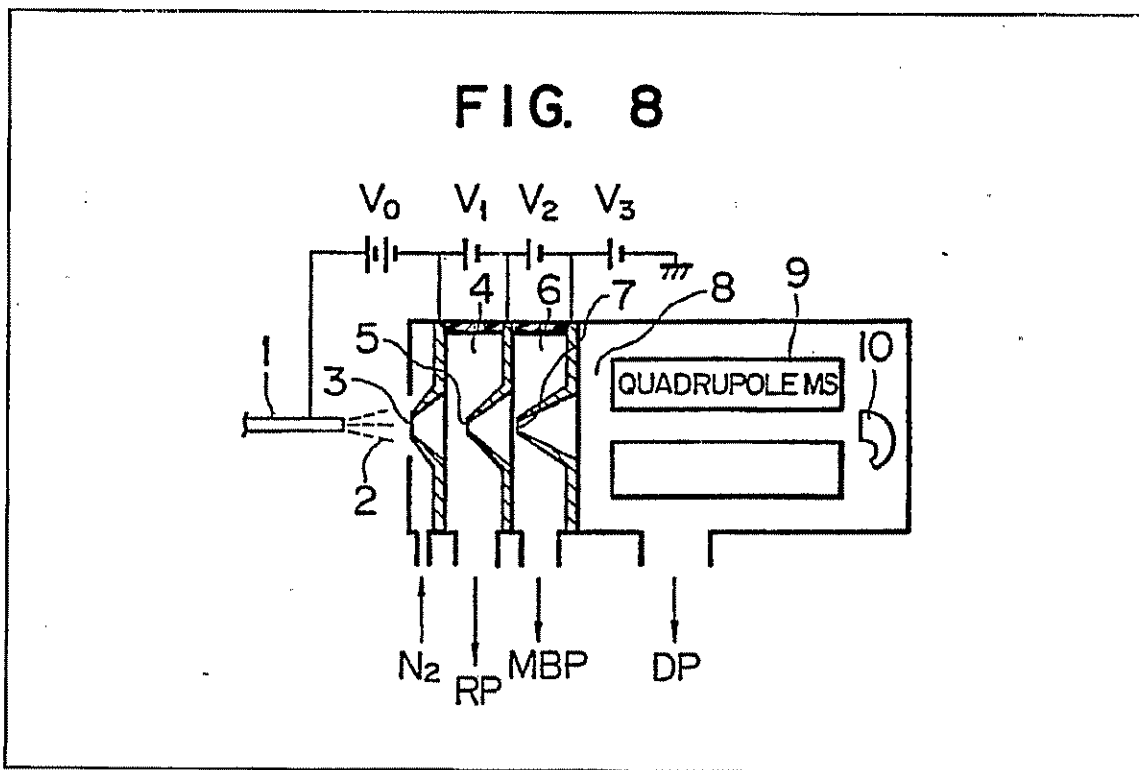
Kambara's teachings have been implemented by numerous other workers since 1977. For example, Chowdhury describes a mass spectrometer system with an electrospray ion source in which "solvent molecules that adhere to the biomolecule ions of interest are removed by collisional activation" by being subjected to an electrostatic field between the capillary tube from which they emerge into the initial vacuum region of the instrument and a downstream skimmer. *See* Chowdhury, col. 5:27-31. Chowdhury discusses adjustment of the field strength to produce dissociation of solvent adduct ions without fragmenting the sample ions:

[C]ollisional activation caused by an electrostatic field 32 in a region of reduced pressure brings about the removal of solvent molecules adhering to the biomolecule ions. *This electrostatic field 32 is easily variable and provides sufficiently fine control of the collisional activation so that at low fields complete desolvation of the molecule ions can be effected without fragmentation*

Chowdhury, col. 5:51-60 (emphasis added).

Kleintop likewise teaches dissociation of solvent adduct ions by placing a DC offset voltage between two electrodes, such as a capillary and skimmer combination: “One method to overcome the loss of desolvating power at low capillary temperatures is by using in-source CAD to promote solvent declustering in the capillary/skimmer region of the interface.” Kleintop concludes that a tube lens voltage may be used “to promote solvent declustering . . . in the capillary skimmer region of the interface.” Kleintop at 905.

Kato teaches dissociation of solvent adduct ions prior to entry into a mass analyzer by application of DC offset voltages to the first and second (3, 5), or the second and third (5, 7), or both pairs, of three successive skimmers that define two serial vacuum chambers (4, 6) directly preceding a mass analyzer (9), as illustrated in Fig. 8 from Kato below:



Kato, like Kambara, identifies pressure and applied voltage as “important factors” in

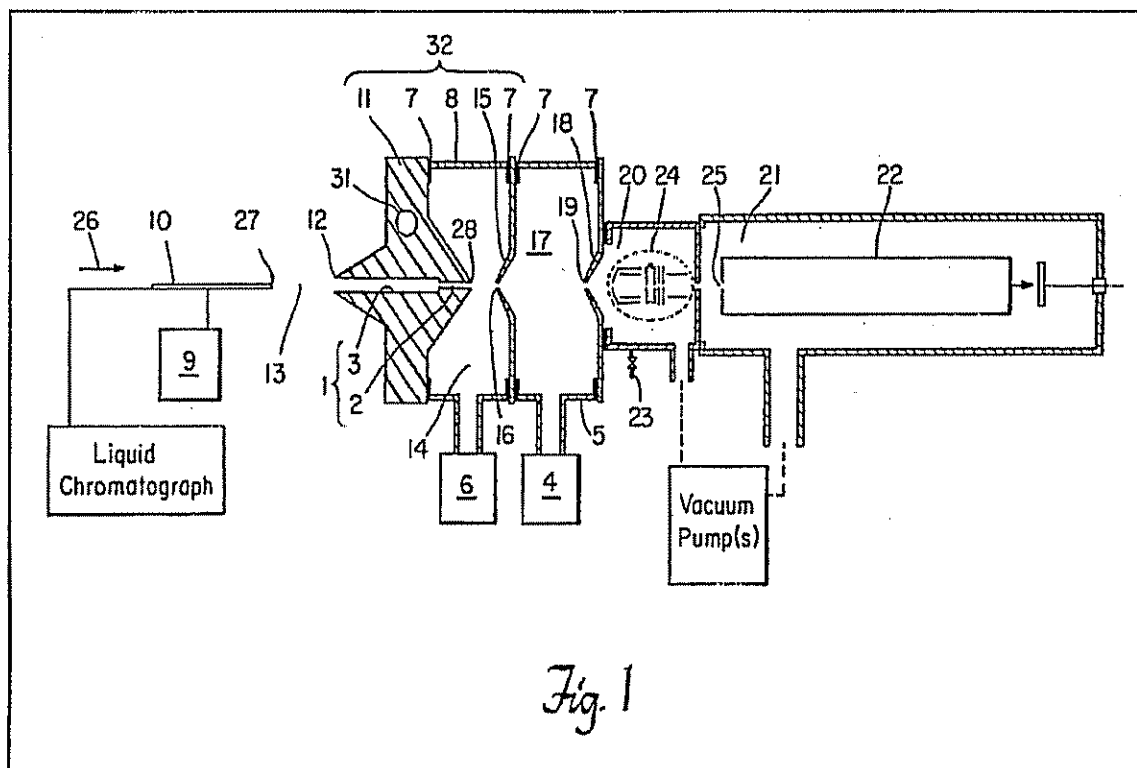
dissociating or converting the adduct ions, and describes his method as "remarkably effective":

Important factors in the desolvation system are a vacuum degree and an intensity of the electric field in the case of the acceleration and collision. Generally, as illustrated in Fig. 8, the electrical potential is applied between the first and second apertures 3, 5 or/and between the second and third apertures 5, 7 whereby the ions are accelerated and collide with the neutral molecules. A degree of the desolvation can be changed by controlling the applied voltages V_1 , V_2 . This method is remarkably effective in the desolvation.

Kato, col. 7:18-28, Fig. 8 (emphasis added).

Tomany, like Kato, teaches dissociation of solvent adduct ions in serial vacuum stages.

Figure 1, reproduced below, shows a mass spectrometer system having an ESI ion source and four vacuum chambers 14, 17, 20 and 21, the last of which contains the mass analyzer (22):



DC offset voltages are applied to produce electric fields between the structural components that define chambers 14 and 17, i.e., fields exist between housing 11 and skimmer

15, and between skimmer 15 and skimmer 18. Tomany, col. 5: 8-11, 33-37. Tomany explains that collisional dissociation is implemented in both chamber 14 and chamber 17:

Because collisions between charged ion stream components (e.g., ions, charged droplets, charged clusters and solvated ions) and neutral molecules occur in region 14 as the ion stream traverses region 14 on its way to skimmer 15, additional desolvation, ion evaporation and declustering occur. *The energy of these collisions can be affected by the potential difference between the housing 11 and skimmer 15.*

* * *

Region 17 is maintained at a lower pressure, typically 0.1-3 Torr by another rotary pump 4. Again, because collisions between the ion stream components (e.g. charged droplets, charged clusters and solvated ions) and neutral gas molecules occur in this region 17 as the ion stream traverses it on its way to skimmer 18, additional desolvation and ion evaporation occurs. *Because of the lower pressure in this region, the energy of these collision is considerably affected by the potential difference between skimmer 15 and skimmer 18 such that considerable desolvation and ion evaporation may occur.*

Tomany, col. 5:11-19, 26-37 (emphasis added).

2. The Implementation of Collisional Dissociation Using a Multipole Ion Guide and a Preceding Lens as Electrodes Was Well-Known as of 1999

It was well-known as of 1999 to dissociate solvent adduct ions by applying a DC offset voltage between a multipole ion guide and a preceding lens. This implementation of the collisional dissociation technique was included in the commercially available TAGA 6000E instrument. In 1989, Smith reported on his experiments using both the commercial TAGA 6000E and a modified version. The commercial TAGA 6000E included a single cryogenically pumped vacuum chamber housing a quadrupole ion guide (Q0) preceding a typical triple quadrupole tandem mass analyzer (Q1, Q2, Q3). Smith 54, Figure 1 (showing modified version with additional vacuum stage). Ions were produced by an ESI source. *Id.* The pressure of the single cryogenically pumped vacuum chamber was in the range of $10^{-6} - 10^{-5}$ torr. *Id.* With regard to the commercial TAGA 6000E, Smith investigated the dissociation of solvent adduct

ions produced by the offset voltage between the orifice (Or) and the quadrupole ion guide (Q0).

Smith found that under typical operating condition, solvent adduct ions were essentially eliminated:

Figure 3 gives ESI mass spectra of horse heart cytochrome c, a protein of Mr 12,360. The spectra were obtained with the unmodified TAGA 6000E ion-sampling orifice, with which the electric field in the atmosphere-vacuum region results only from the voltage difference between the orifice and the rf-only quadrupole lens, $\Delta(\text{Or-Q0})$. As shown in Figure 3a, when $\Delta(\text{Or-Q0}) = 0$ V, the cytochrome c molecular ion peaks exhibit substantial tailing to higher m/z, which is attributed to unresolved adduction or solvent association. *Under typical operating conditions, with $\Delta(\text{Or-Q0})$ of typically +5-40 V chosen to optimize desolvated molecular ion intensity, solvent association is essentially eliminated....*

Smith at 56 (emphasis added).

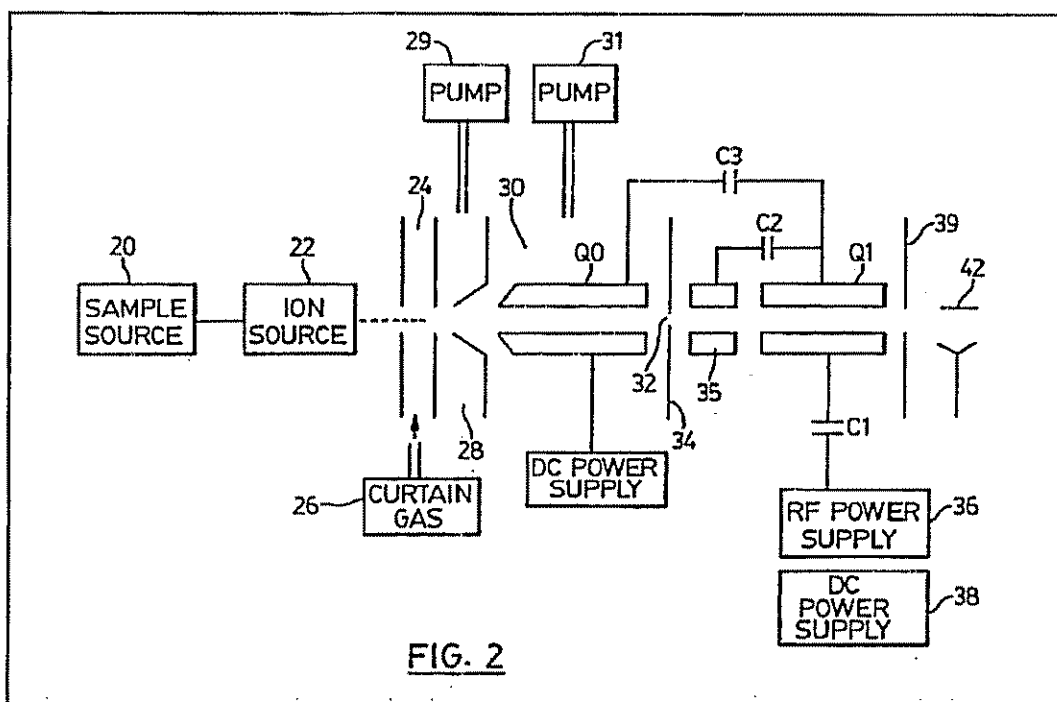
The essentially complete conversion of adduct ions by collisional dissociation that Smith observed in the ion guide of the TAGA 6000E occurred under conditions that are within the ranges of pressures and offset voltages specified for conversion of adduct ions in the second ion guide chamber in the '784 patent. The '784 patent states that the pressure in the second ion guide chamber is "more preferably below 0.5 mTorr" (col. 4:50) and that the "DC offset voltage range for efficient solvent adduction conversion should be ± 10 to ± 30 Volts." '784, col. 4:50; col. 6:59-60. In the TAGA 6000E system, the pressure in the vacuum chamber housing the multipole ion guide (Q0) was of "the order of 10^{-6} to 10^{-5} torr," which is below 0.5 mTorr. Smith, 54. The DC offset voltage between the orifice (Or) and Q0 that was effective to convert adduct ions, which Smith characterized as "typical operating conditions," was 5-40 V, which encompasses the range in the '784 patent. Smith at 56.

There are numerous other instances of the use of a multipole ion guide as a counter-electrode for purposes of collisional dissociation prior to 1999. For example, Thomson describes a mass spectrometer system (sold commercially under the name API III) in which dissociation of

adduct ions was accomplished by applying a DC offset voltage between the inlet orifice and a quadrupole ion guide. Thomson states that in the API III, “[t]he declustering region is between the orifice and the RF-only transfer rods (‘Q0’),” and that “[t]he potential between OR and Q0 controls declustering and fragmentation.” Thomson at 1092.

In addition to describing dissociation of adduct ions using a DC offset between an orifice and a quadrupole ion guide, Thomson also describes dissociation, without fragmentation, in the last of a series of three RF-only quadrupoles immediately preceding a quadrupole mass filter. He describes an experiment conducted with the API III, which was a triple quadrupole mass spectrometer (i.e., a mass spectrometer having a three stage mass analyzer consisting of a quadrupole mass filter (Q1), followed by an RF-only quadrupole collision cell (Q2), followed by a second quadrupole mass filter (Q3)). In the experiment, Q1 was operated in RF-only mode and thus Q0 (the ion guide), Q1 and Q2 were RF-only quadrupoles. No declustering offset voltage was applied between the orifice and Q0, but instead declustering was accomplished in Q2 by virtue of the Q2 rod offset voltage. Thomson notes that adduct ions were dissociated without fragmentation: “for each charge state there is an optimum voltage for declustering without fragmentation.” *Id.* Thus it was known prior to 1999 that in a mass spectrometer having more than one RF-only quadrupole, adduct ions could be dissociated by applying an appropriate DC offset voltage between any one or more of the RF-only quadrupoles and a preceding lens.

Hager also describes the application of a DC offset voltage between an inlet orifice (a skimmer in this instance) and a multipole ion guide for dissociating solvent adduct ions. In Hager’s mass spectrometer system, two vacuum chambers precede the mass analyzer (Q1) chamber, as shown in Figure 2 (reproduced below).



In the first vacuum chamber (28), an offset voltage exists between the entrance orifice and the skimmer (defining chamber 28). In addition, another offset voltage exists between the skimmer and the quadrupole ion guide (Q0) in chamber 30. These offset voltages produce collisional dissociation in both chambers. Hager describes this method as "conventional":

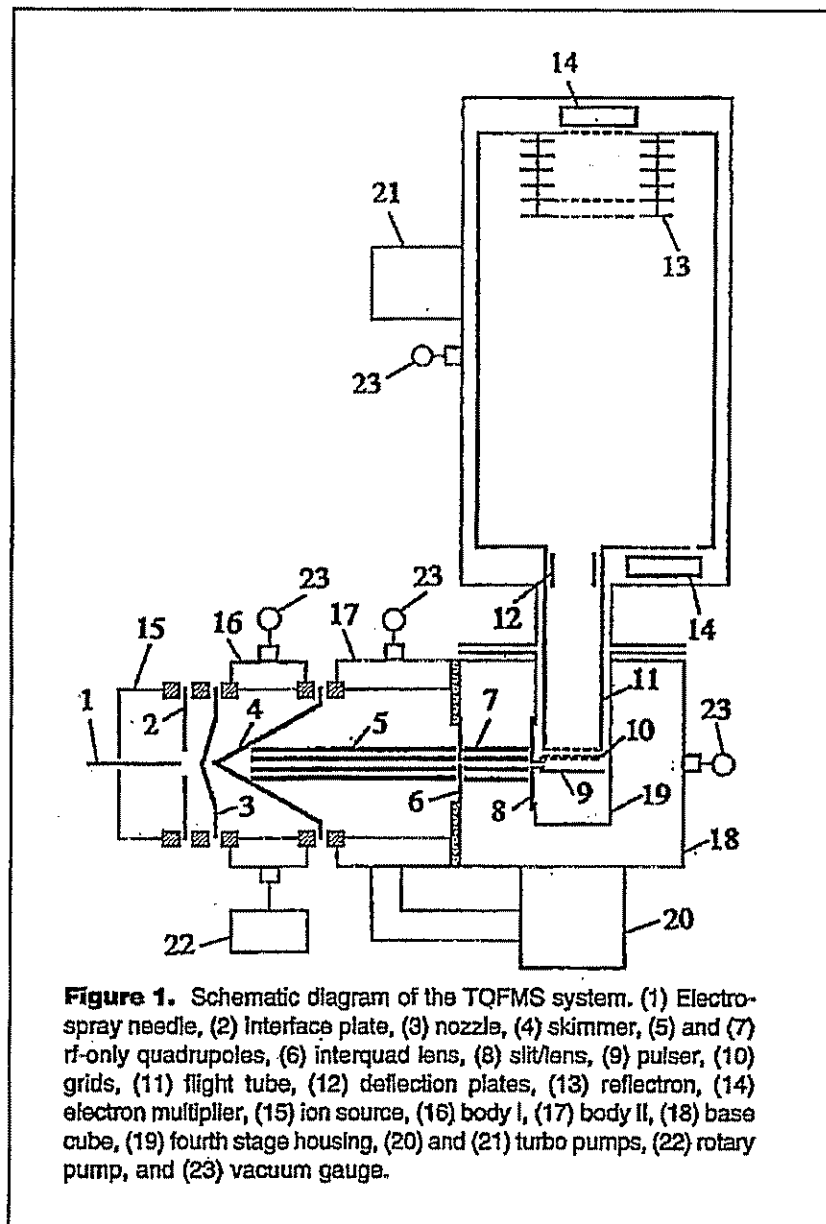
Various stages of declustering are commonly used to reduce this mixture of ionic species to a larger proportion of bare monomer ions to solvated ions.

Conventional declustering methodologies include . . . collisional dissociation by acceleration of the ions through relatively high pressure regimes using voltage gradients between the orifice and skimmer and between the skimmer and Q0.

Hager, col. 10:48-56 (emphasis added).

3. Multistage Multipole Ion Guide Interfaces Were Well-Known as of 1999

Mass spectrometers systems employing multiple ion guides in separate vacuum chambers to interface an API source with a mass analyzer were well-known as of 1999. Lazar describes such a mass spectrometer system, depicted in his Figure 1 (reproduced below):



Lazar's Figure 1 shows a mass spectrometer having an ESI source (1), an interface plate (2), a nozzle (3), a skimmer (4) and two consecutive RF-only ion guides (5) and (7) separated by an interquad lens (6). The second ion guide (7) is followed by a lens (8). Lazar, Figure 1, at 3206. The Lazar mass spectrometer includes four vacuum regions: "The first and second

vacuum stages are separated by a skimmer (4).” *Id.* at 3206. The second stage includes the first RF-only ion guide (5). *Id.* “The third vacuum stage . . . houses the second set of rf-only quadrupole rods” and the fourth stage houses the time of flight (“TOF”) mass analyzer. *Id.*

Lazar attempted to find optimal pressures for operation of the ion guides, including a configuration that yielded pressures of “3 Torr in the first stage, 1.5×10^{-1} Torr in the second stage, 7×10^{-6} Torr in the third stage, and $(3-4) \times 10^{-7}$ Torr in the fourth stage.” *Id.* at 3207. Lazar also experimented with voltages along the ion path, including the voltages between skimmer (4) and the first RF-only ion guide and the interquad lens (6) and the second RF-only ion guide to optimize the intensity of the ion signal:

We also monitored the signal intensity as a function of the voltage applied to each ion optics element. A very strong dependence was found for the skimmer, rods offset, and interquad lens voltage. These elements control the ion energy in the high pressure collisional focusing region of the first set of rods. . . . Maximum intensity signals are observed for each compound at different voltage settings.

Id. at 3208, col. 2 (emphasis added). *See also*, Figure 2 at p. 3208 depicting the DC offset voltage in the second ion guide.

Thus, Lazar discloses:

- two sequential multipole ion guides, with each ion guide in its own vacuum chamber;
- variable DC voltage lenses which precede each ion guide;
- a pressure of 1.5×10^{-1} Torr in the first ion guide chamber (second vacuum stage); and
- a lower pressure of and 7×10^{-6} Torr in the second ion guide chamber (third vacuum stage).

There are numerous other examples of mass spectrometers having two or more multipole ion guides in separate vacuum chambers at different pressures in the art prior to 1999. For example, Buchanan describes a mass spectrometer system including an electrospray ion source at

atmospheric pressure, three octapole ion guides, and a Fourier transform ion cyclotron resonance (FTICR) mass analyzer. The octapole ion guides are in separate differentially pumped vacuum chambers. The second and third octapoles have variable “independent DC offset voltages.” Buchanan at 518. Buchanan reports on tests to establish “initial operating conditions to allow the system to be optimized” in which it was found that “a small positive DC offset applied to octapole #2 (behind the skimmer) and a small negative dc offset on octapole #3 has yielded the best signal.” *Id.*

Similarly, Beu describes a mass spectrometer employing electrospray ionization and having three quadrupole ion guides, each in a separately pumped vacuum chamber. Potentials are applied along the ion path defined by the ion guides “to provide acceleration of ions between quadrupoles.” Beu at 559.

A mass spectrometer having a double ion guide consisting of hexapoles in separate differentially pumped vacuum chambers is disclosed by Jarvis. The double ion guide interfaces an electrospray ion source with a time of flight mass analyzer. Jarvis at 1193.

C. Detailed Explanation of the Manner of Applying the Cited Prior Art to Every Claim

Applera submits that each of the claims of the '784 patent is unpatentable either because its subject matter is anticipated by prior art or would have been obvious to the person of ordinary skill in the art in view of the teachings of the prior art.

The claims are directed to the mere use of a well-known technique for converting solvent adduct ions to sample ions in a well-known mass spectrometer system architecture. Mass spectrometer systems in which an API source is coupled to a mass analyzer using multiple differentially pumped vacuum chambers each including a multipole ion guide were well-known in the art as of 1999. The application of a variable DC offset voltage between each ion guide and

the preceding lens in such systems was also well-known. The double ion guide TOF mass spectrometer system of Lazar exemplifies such systems.

The phenomenon of solvent adduct ion formation in mass spectrometer systems using an API source, particularly electrospray, was well-known prior to 1999. The technique of converting adduct ions to sample ions by collisional dissociation was also well-known by 1999. In 1977, Kambara described conversion of cluster ions by collisional dissociation, and the parameters (primarily pressure and voltage) that affect the outcome. Others in the field had described the conversion of adduct ions by collisional dissociation through application of a DC offset voltage between a lens element and a multipole ion guide prior to 1999. Indeed, in 1989, Smith reported the conversion of adduct ions by collisional dissociation in the ion guide of a commercially available mass spectrometer system (TAGA 6000E) under conditions that are within the ranges of pressures and offset voltages specified for conversion of adduct ions in the second ion guide chamber in the '784 patent.

In the charts set forth below, Applera demonstrates how the prior art teaches each and every element of the claims of the '784 patent. Applera primarily cites Lazar, Smith and Hager in the charts, but numerous other prior art references, discussed above and below, render the claims unpatentable as well.

1. Claims 1 and 2 Are Unpatentable as Obvious Over Lazar in View of Smith, or Hager in View of Lazar, or Buchanan in View of either Smith or Thomson

Claim 1	Lazar/Smith
A mass spectrometer system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through intermediate vacuum chambers in which sample ions and solvent molecules form adduct ions with a reduction of	Lazar discloses a mass spectrometer system including a time of flight ("TOF") mass analyzer disposed in its fourth vacuum stage at a high vacuum pressure of $3-4 \times 10^{-7}$ Torr. (Figure 1; 3207). The mass spectrometer system is used to analyze sample ions formed at atmospheric pressure by an ESI source

sample ion current including:	(Figure 1, items 1 and 15 at p. 3206). The ions are directed from the ion source to the TOF mass analyzer through three intermediate vacuum chambers. (3206, 3207). Sample ions and solvent molecules form adduct ions with a reduction of ion current. Lazar specifically notes the formation of adducts in one of his experiments: "However, the paraquat spectrum was mainly composed of a series of <i>ion clusters</i> . The signal intensity at 93 <i>m/z</i> was extremely weak and dependent on the first quadrupole offset voltage." (3208; emphasis added).
first and second evacuated chambers directly preceding the mass analyzer chamber with the first chamber being at a higher pressure than the second chamber,	In Lazar's system, two vacuum chambers, denominated the "second vacuum stage" and the "third vacuum stage" directly precede the TOF mass analyzer chamber. (Figure 1; 3206-3207). The first of these two chambers is at a higher pressure (1.5×10^{-1} Torr) than the second of them (7×10^{-6} Torr). (3207).
a first multipole ion guide in the first chamber for guiding ions into said second chamber,	Lazar's system includes a first multipole ion guide in the first chamber for guiding ions into the second chamber. (See, e.g., 3206 ("The ion beam entering the second stage is subsequently passed through the first set of rf-only quadrupoles (5).") and 3207 ("ions are pulled out from the first set of rods and introduced into the third vacuum stage, which houses the second set of rf-only quadrupole rods (7).").
a second multipole ion guide in the second chamber for guiding ions from the first chamber into the high vacuum chamber for mass analysis, and	Lazar's system includes a second multipole ion guide in a second chamber ("third vacuum stage") for guiding ions from the first chamber into the high vacuum chamber ("fourth vacuum stage") for mass analysis. (See, e.g., Figure 1; 3207 ("The third vacuum stage was necessary since the direct passage from the high-pressure region ($10^{-1} - 10^{-3}$ Torr) of the second stage to the desired low-pressure region of the fourth stage (10^{-7} Torr) was not possible with the current pumping system."). The "fourth vacuum stage" houses the TOF mass analyzer. (Figure 1).
means associated with one or both of said first and second multipole ion guides for increasing the translational kinetic energy of the adduct ions so that at the vacuum pressure of the	There is an adjustable DC offset voltage between each of the two multipole ion guides and the preceding lens in Lazar's system, each of which can increase the translational kinetic

<p>second interface chamber adduct ions traveling into the chamber are converted into sample ions without fragmentation of sample ions whereby to increase the sample ion current and therefore the sensitivity of the mass spectrometer system.</p>	<p>energy of adduct ions. (3208: "We also monitored the signal intensity as a function of the voltage applied to each ion optics element. A very strong dependence was found for the skimmer, <i>rods offset</i>, and interquad lens voltage." (Emphasis added). See also Figure 2 at 3208 (showing the offset voltage of the second ion guide ("Off2") as 30 V.) Thus, Lazar employs the "means" described in the specification of the '784 patent.</p> <p>Smith describes conversion of solvent adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of Lazar. (Smith at 56 (1st col.)). The pressure of Smith's chamber is of "the order of 10^{-6} to 10^{-5} torr" and the pressure of Lazar's second ion guide chamber is 7×10^{-6} torr. (Smith at 54 (2nd col.); Lazar at 3207).</p>
<p>Claim 2</p>	<p>Lazar/Smith</p>
<p>A mass analyzer as in claim 1 including ion lenses preceding each said multipole ion guide and a DC voltage is applied between a selected lens and its associated ion guide to increase the translational kinetic energy of the adduct ions entering the second interface chamber.</p>	<p>Skimmer (4) precedes the first ion guide and "interquad lens" (6) precedes the second ion guide. There is an adjustable DC offset voltage between each of the two multipole ion guides and the preceding lens in Lazar's system, each of which can increase the translational kinetic energy of adduct ions. (3208; Figure 2).</p>

The charts show that Lazar discloses each of the elements of claims 1 and 2, except the adjustment of the DC offset voltage in his second ion guide chamber specifically to convert solvent adduct ions to sample ions. It was well-known to those skilled in the art to convert solvent adduct ions to sample ions in ion guide chambers at various pressures by adjusting the DC offset voltage appropriately. It would have been obvious in view of Smith to adjust the DC offset voltage of Lazar's second ion guide appropriately to convert adduct ions where present to sample ions at the similar pressure of Lazar's second ion guide chamber without fragmentation of the sample ions. The person of ordinary skill in the art as of 1999 would have been motivated

to do so and would have expected success on the basis of his understanding of the collisional dissociation technique for converting adduct ions to sample ions and the well-known implementation of the technique using a DC offset voltage between a multipole ion guide and a preceding lens. Therefore, claims 1 and 2 are unpatentable over Lazar in view of Smith under 35 U.S.C. § 103.

Claim 1 and 2 are unpatentable based on the combined teachings of other references as well. As shown in the following chart, Hager discloses each element of claims 1 and 2 except the inclusion of an ion guide in the first of the two successive vacuum chambers that precede the mass analyzer. However, Lazar discloses two successive ion guide stages preceding a mass analyzer.

Claim 1	Hager/Lazar
A mass spectrometer system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through intermediate vacuum chambers in which sample ions and solvent molecules form adduct ions with a reduction of sample ion current including:	Hager discloses a mass spectrometer system (Fig. 2 or Fig. 10a) including a mass analyzer (quadrupole mass analyzer Q1 in Fig. 2; triple quadrupole analyzer in Fig. 10a) in a high vacuum chamber for analyzing sample ions formed at atmosphere (col. 5: 47-5: ESI source or ion spray source) and directed through intermediate vacuum chambers (col. 5: 53-58: chamber 28 pumped by pump 29 to a pressure of 2 torr and chamber 30 pumped by pump 31 to a pressure of 8×10^{-3} torr). Hager states that “[i]ons generated by electrospray ionization techniques may enter the vacuum chamber as monomers, monomers clustered with solvent molecules, and possibly multimers with and without solvent molecules attached.” (Col. 10:45-48).
first and second evacuated chambers directly preceding the mass analyzer chamber with the first chamber being at a higher pressure than the second chamber,	In Hager’s system, two vacuum chambers (chamber 28 and chamber 30) directly precede the analyzer chamber, with chamber 28 at a higher pressure than chamber 30 (2 torr versus 8×10^{-3} torr). Lazar’s system also includes two vacuum chambers directly preceding an analyzer, the

	first of which is at a higher pressure than the second (1.5×10^{-1} Torr versus 7×10^{-6} torr (which is below the pressure of 1 mTorr specified in the '784 patent)).
a first multipole ion guide in the first chamber for guiding ions into said second chamber,	Lazar's system includes a first ion guide (5) in a first chamber for guiding ions into a second chamber that includes a second ion guide (7).
a second multipole ion guide in the second chamber for guiding ions from the first chamber into the high vacuum chamber for mass analysis, and	In Hager's system, chamber 30 includes quadrupole ion guide Q0 for guiding ions from chamber 28 to the analyzer chamber. (Col. 5:53-58).
means associated with one or both of said first and second multipole ion guides for increasing the translational kinetic energy of the adduct ions so that at the vacuum pressure of the second interface chamber adduct ions traveling into the chamber are converted into sample ions without fragmentation of sample ions whereby to increase the sample ion current and therefore the sensitivity of the mass spectrometer system.	Hager discloses adding translational kinetic energy to the adduct ions as they travel through the chambers 28 and 30 by applying DC offset voltages between the orifice and skimmer in chamber 28 and between the skimmer and Q0 in chamber 30 such that adduct ions are dissociated in the chamber 30. Hager states: "Various stages of declustering are commonly used to reduce this mixture of ionic species to a larger proportion of bare monomer ions to solvated ions. Conventional declustering methodologies include . . . collisional dissociation by acceleration of the ions through relatively high pressure regimes using voltage gradients between the orifice and skimmer and between the skimmer and Q0." (Col. 10:51-56).
Claim 2	Hager/Lazar
A mass analyzer as in claim 1 including ion lenses preceding each said multipole ion guide and a DC voltage is applied between a selected lens and its associated ion guide to increase the translational kinetic energy of the adduct ions entering the second interface chamber.	<p>In Hager's system, an ion lens precedes a skimmer in the first vacuum stage and a DC voltage is applied between the lens and the skimmer, and an ion lens (the skimmer) precedes a quadrupole ion guide in the second vacuum stage and a DC voltage is applied between lens and the ion guide. The DC voltage between the skimmer and the quadrupole ion guide increases the translational kinetic energy of adduct ions entering the second chamber. (Fig. 2; Col. 10:51-56).</p> <p>In Lazar's system, skimmer (4) precedes the first ion guide and "interquad lens" (6) precedes the second ion guide. There is an adjustable DC offset voltage between each of</p>

	the two multipole ion guides and the preceding lens, each of which can increase the translational kinetic energy of adduct ions. (Fig. 1; 3208).
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It would have been obvious to a person skilled in the art as of 1999 in view of Lazar's teaching of a double ion guide interface to add a multipole ion guide to the first vacuum chamber of Hager and apply the DC voltage between the entrance orifice (lens) and the ion guide, as in the first ion guide chamber of Lazar. The person skilled in the art would have been motivated to do so and would have expected success based on his knowledge of the well-known advantages of multipole ion guides for containing and transmitting ions through differentially pumped vacuum stages in a multistage interface, as exemplified by Lazar.

Claims 1 and 2 are also unpatentable over the combined teachings of Buchanan and either Smith or Thomson. Like Lazar, Buchanan discloses a mass spectrometer system in which multiple vacuum chambers each containing a multipole ion guide (octapoles 1, 2, 3) provide the interface between an atmospheric pressure ion source (ESI) and a mass analyzer (FTICR mass analyzer disposed in a vacuum chamber at 10^{-8} and 10^{-9} torr). The ions and solvent molecules form adducts upon entering in the vacuum region which can reduce sample ion current. The two vacuum chambers in which octapoles #2 and #3 are present immediately precede the mass analyzer chamber, and the pressure in the octapole #2 chamber (10^{-4} torr) is higher than the pressure of the octapole #3 chamber (10^{-6} torr). Octapole #2 guides ions into the vacuum chamber containing octapole #3. Octapole #3 guides ions from the chamber containing octapole #2 into the high vacuum chamber for mass analysis. Octapoles #2 and #3 each have variable DC offset voltages that can be set to increase the translational kinetic energy of adduct ions. Buchanan thus discloses each of the elements of claim 1 except that Buchanan does not explicitly state that DC offset voltage in the octapole #3 ion guide chamber may be adjusted

appropriately to convert any adduct ions present to sample ions.

As noted above, Smith describes conversion of adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the octapole #3 ion guide chamber of Buchanan. (Smith at 56 (1st col.)). The pressure of Smith's chamber is of "the order of 10^{-6} to 10^{-5} torr" and the pressure of octapole #3 ion guide chamber is 10^{-6} torr. (Smith at 54 (2nd col.); Buchanan at 518). Alternatively, Thomson teaches that in a mass spectrometer having more than one multipole ion guide, adduct ions can be converted to sample ions by applying an appropriate DC offset voltage between any one or more of the RF-only quadrupoles and its preceding lens. Thomson specifically described declustering solvent adducts, without fragmentation, in the last of a series of RF-only quadrupoles that immediately precedes a mass analyzer. The person of ordinary skill in the art as of 1999 would have been motivated to combine the teachings of Buchanan and either Smith or Thomson to adjust the DC offset voltage in the octapole #3 ion guide chamber appropriately to convert any adduct ions present to sample ions and would have expected success on the basis of his understanding of the collisional dissociation technique for converting adduct ions to sample ions and the well-known implementation of the technique using a DC offset voltage between a multipole ion guide and a preceding lens. Therefore, claims 1 and 2 are unpatentable over Buchanan in view of either Smith or Thomson under 35 U.S.C. § 103.

2. Claim 3 is Unpatentable as Anticipated by Any of Smith, Kambara, Chowdhury, Kato, Klientop, Thomson, Tomany or Hager

Claim 3	Smith
A method of mass analyzing sample ions produced at atmospheric pressure and introduced into a mass analyzer disposed in a vacuum chamber, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions	Smith describes a method of mass analyzing sample ions in the TAGA 6000 mass spectrometer system, in which ions are produced at atmospheric pressure by an electrospray ion source and introduced into a mass analyzer (Q1 and/or Q3 mass analyzing

comprising the step of	quadrupoles) disposed in a vacuum chamber (vacuum chamber at 10^{-6} to 10^{-5} torr). Smith describes the existence of solvent adduct ions in the TAGA 6000 mass spectrometer system with the DC offset voltage between the multipole ion guide (Q0) and preceding lens (Or) set to 0, and the consequent reduction of sample ions. (56 (1 st col.): "when $\Delta(\text{Or-Q0}) = 0$ V, the cytochrome c molecular ion peaks exhibit substantial tailing to higher m/z, which is attributed to unresolved adduction or solvent association.")
dissociating the adduct ions prior to entry into the mass analyzer to form sample ions to increase the sample ion current entering into the mass analyzer.	Smith describes dissociation of the adduct ions prior to entry into the mass analyzer when the DC offset voltage is adjusted to 5-40 V. ((56 (1 st col.): "Under typical operating conditions, with $\Delta(\text{Or-Q0})$ of typically +5-40 V chosen to optimize desolvated molecular ion intensity, solvent association is essentially eliminated. . . .")

Smith anticipates the single step method of claim 3. Other references likewise anticipate claim 3. Each of Kambara, Chowdhury, Kato, Klientop, Thomson, Tomany and Hager discloses use of a mass analyzer housed in vacuum chamber for the mass analysis of sample ions produced at atmospheric pressure. Kambara, 130, Fig. 1; Chowdhury, col. 5:39-45, Fig. 1 (31); Kato, col. 7: 34-36, Fig. 8 (8); Klientop, 905, Fig. 1; Thomson, 1092; Tomany, col. 5: 54-63, Fig. 1 (21, 22); Hager, col. 5: 63-67, Fig. 2. Each of these references discloses the well-known problem of solvent adduct ion formation. Kambara, 130; Chowdhury, col. 2: 19-24, col. 5: 27-31; Kato, col. 4:61 – col. 5: 6, col. 5: 20-22; Klientop, 905; Thomson, 1092; Tomany, col. 5: 11-16; Hager, col. 10: 45-51. Each of these references discloses dissociation of adduct ions prior to entry into the mass analyzer to increase the sample ion current entering the mass analyzer. Kambara, 135 (discussing dissociation of cluster ions to "molecular or quasi-molecular ions" prior to entering the mass analyzer); Chowdhury, col. 3: 54-58 ("The ions exit into a vacuum chamber where solvent is further removed by collisional activation and then the charged ions pass through the

hole in the skimmer, through the holes in the lenses and baffle and into the analyzer.”), col. 5: 49-63; Kato, col. 7:18-28 and Fig. 8; Klientop, 905 (under “Results”: “The mass spectra of Figures 2b demonstrate a significant increase in molecular ion production using . . . higher tube lens voltages . . .”); Thomson, 1092 (col. 2: “Thus for each charge state there is an optimum voltage for declustering without fragmentation”); Tomany, col. 5: 11-19, 26-37 (discussing the desolvation that occurs in chambers 14 and 17); Hager, col. 10: 51-58 (“ion acceleration techniques . . . often result in spectra dominated by predominantly declustered ions”).

Therefore, claim 3 is unpatentable as anticipated by any one of Smith, Kambara, Chowdhury, Kato, Klientop, Thomson, Tomany or Hager.

3. Claims 4-8 are Unpatentable as Obvious Over Lazar in View of Smith, or Hager in View of Lazar, or Buchanan in View of either Smith or Thomson

Claim 4	Lazar/Smith
The method of operating a mass spectrometer system including a mass analyzer which analyzes sample ions formed at atmospheric pressure, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions, said system including first and second multipole ion guides disposed in serial first and second evacuated chambers separated by an ion lens for guiding analyte ions into said mass analyzer and an ion lens defining the first evacuated chamber which comprises	Lazar discloses a method of operating a mass spectrometer system including a time of flight (“TOF”) mass analyzer (Figure 1, items 9-14; 3206-07) which analyzes sample ions formed at atmospheric pressure by an ESI source (Figure 1, items 1, 15; 3206). Sample ions and solvent molecules form adduct ions with a reduction of ion current. Lazar specifically notes the formation of adduct ions: “However, the paraquat spectrum was mainly composed of a series of ion clusters. The signal intensity at 93 <i>m/z</i> was extremely weak and dependent on the first quadrupole offset voltage.” (3208). Lazar’s system includes two serial vacuum chambers separated by an ion lens (“interquad lens” 6 in Fig. 1) each of which contains an RF-only quadrupole ion guide (5,7 in Fig. 1) for guiding ions into the mass analyzer. An ion lens (skimmer 4 in Fig. 1) defines the first of the two ion guide chambers. (Figure 1; 3206-3207).
applying a DC offset voltage between a selected one or both lenses and the succeeding	An adjustable DC offset voltage is applied between each of the two multipole ion guides

<p>multipole ion guide having an amplitude so as to provide translational kinetic energy to said adduct ions to dissociate the adduct ions without dissociating sample ions at the pressure of the second chamber to increase the sample ion current and the sensitivity of the mass spectrometer system.</p>	<p>and the preceding lens in Lazar's system, each of which can provide translational kinetic energy to adduct ions. (3208: "We also monitored the signal intensity as a function of the voltage applied to each ion optics element. A very strong dependence was found for the skimmer, <i>rods offset</i>, and interquad lens voltage." See also Figure 2 at 3208 (showing the offset voltage of the second ion guide ("Off2") as 30 V.)</p> <p>Smith describes dissociation of adduct ions without dissociating sample ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of Lazar. (Smith at 56 (1st col.)). The pressure of Smith's chamber is of "the order of 10^{-6} to 10^{-5} torr" and the pressure of Lazar's second ion guide chamber is 7×10^{-6} torr. (Smith at 54 (2nd col.); Lazar at 3207).</p>
<p>Claim 5</p>	<p>Lazar/Smith</p>
<p>A mass spectrometer system as in claim 4 in which the pressure in the first chamber is below 500 mTorr, and in the second chamber is below 1 mTorr, and the offset voltage applied between the interchamber lens and the second multipole ion guide is between ± 10 volts and ± 30 volts.</p>	<p>The pressure in Lazar's first chamber ("second vacuum stage") is below 500 mTorr (1.5×10^{-1} Torr) and the pressure in the second chamber ("third vacuum stage") is below 1 mTorr (7×10^{-6} Torr). There is an adjustable DC offset voltage between the "interquad lens" (6) and the second quadrupole ion guide. (Fig. 1, 3206, 3297, 3208).</p> <p>Smith describes conversion of adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of Lazar. (56 (1st col.))</p>
<p>Claim 6</p>	<p>Lazar/Smith</p>
<p>A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less than 250 mTorr, and in the second chamber is less than 0.7 mTorr.</p>	<p>The pressure in Lazar's first chamber is below 250 mTorr (1.5×10^{-1} Torr) and the pressure in the second chamber is below 0.7 mTorr (7×10^{-6} Torr. (Fig. 1, 3206, 3207).</p>
<p>Claim 7</p>	<p>Lazar/Smith</p>
<p>A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less</p>	<p>The pressure in Lazar's first chamber is below 175 mTorr (1.5×10^{-1} Torr) and the pressure in</p>

than 175 mTorr, and in the second chamber is less than 0.5 mTorr.	the second chamber is below 0.5 mTorr (7×10^{-6} Torr. (Fig. 1, 3206, 3207).
Claim 8	Lazar/Smith
A mass spectrometer as in claim 6 or 7 in which the offset voltage is ± 10 volts.	<p>In Lazar's system, there is an adjustable DC offset voltage between the "interquad lens" (6) and the second quadrupole ion guide. (Fig. 1, 3206, 3297, 3208).</p> <p>Smith describes conversion of adduct ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of Lazar. (56 (1st col.))</p>

The charts above shows that Lazar discloses each of the elements of claims 4-8, except that Lazar does not state that the DC offset voltage in his second ion guide is adjusted specifically to convert solvent adduct ions to sample ions in his second ion guide chamber. It was well-known to those skilled in the art to dissociate adduct ions without dissociating sample ions in ion guide chambers at various pressures by adjusting the DC offset voltage appropriately. It would have been obvious in view of Smith to adjust the DC offset voltage of Lazar's second ion guide appropriately to convert adduct ions where present to sample ions at the similar pressure of Lazar's second ion guide chamber without fragmentation of the sample ions. The person of ordinary skill in the art as of 1999 would have been motivated to do so and would have expected success on the basis of his understanding of the collisional dissociation technique for converting adduct ions to sample ions and the well-known implementation of the technique using a DC offset voltage between a multipole ion guide and a preceding lens.

Therefore, claims 4-8 are unpatentable over Lazar in view of Smith under 35 U.S.C. § 103.

Claim 4	Hager/Lazar
<p>The method of operating a mass spectrometer system including a mass analyzer which analyzes sample ions formed at atmospheric pressure, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions, said system including first and second multipole ion guides disposed in serial first and second evacuated chambers separated by an ion lens for guiding analyte ions into said mass analyzer and an ion lens defining the first evacuated chamber which comprises</p>	<p>Hager discloses a method of operating a mass spectrometer system including a quadrupole mass analyzer (Fig. 1 (Q1); col. 3:63-66) which analyzer ions formed at atmospheric pressure by an ESI or ion spray source (col. 5:47-50). Sample ions and solvent molecules form adduct ions with a reduction of ion current. Hager states that “[i]ons generated by electrospray ionization techniques may enter the vacuum chamber as monomers, monomers clustered with solvent molecules, and possibly multimers with and without solvent molecules attached.” (Col. 10:45-48). Hager’s system includes serial first and second evacuated chambers (Fig. 1: 28, 30) separated by an ion lens (skimmer). Ions are guided through chamber 28 and chamber 30, which contains an RF-only quadrupole ion guide Q0. (Col. 5:53-58).</p> <p>Lazar’s system includes two serial vacuum chambers separated by an ion lens (“interquad lens” 6 in Fig. 1) each of which contains an RF-only quadrupole ion guide (5,7 in Fig. 1) for guiding ions into the mass analyzer. An ion lens (skimmer 4 in Fig. 1) defines the first of the two ion guide chambers. (Figure 1; 3206-3207).</p>
<p>applying a DC offset voltage between a selected one or both lenses and the succeeding multipole ion guide having an amplitude so as to provide translational kinetic energy to said adduct ions to dissociate the adduct ions without dissociating sample ions at the pressure of the second chamber to increase the sample ion current and the sensitivity of the mass spectrometer system.</p>	<p>Hager discloses adding translational kinetic energy to the adduct ions as they travel through the chambers 28 and 30 by applying DC offset voltages between the orifice and skimmer in chamber 28 and between the skimmer and Q0 in chamber 30 such that adduct ions are dissociated in the chamber 30. Hager states:</p> <p>“Various stages of declustering are commonly used to reduce this mixture of ionic species to a larger proportion of bare monomer ions to solvated ions. Conventional declustering methodologies include . . . collisional dissociation by acceleration of the ions through relatively high pressure regimes using voltage gradients between the orifice and skimmer and between the skimmer and Q0.” (Col. 10:51-</p>

	56).
Claim 5	Hager/Lazar
A mass spectrometer system as in claim 4 in which the pressure in the first chamber is below 500 mTorr, and in the second chamber is below 1 mTorr, and the offset voltage applied between the interchamber lens and the second multipole ion guide is between ± 10 volts and ± 30 volts.	<p>The pressures in Hager's first and second vacuum chambers are above 500 mTorr (2000 mTorr in Hager's first chamber) and 1 mTorr (8 mTorr in Hager's second chamber). However, it would have been obvious to use pumps that would achieve slightly lower pressures in these chambers. Hager states that "[c]onventional DC offsets are also applied to the various rods and to the interface plates from the DC power supply 38." (Col. 6:11-12).</p> <p>The pressure in Lazar's first chamber ("second vacuum stage") is below 500 mTorr (150 mTorr) and the pressure in the second chamber ("third vacuum stage") is below 1 mTorr (0.007 mTorr). There is an adjustable DC offset voltage between the "interquad lens" (6) and the second quadrupole ion guide. (Fig. 1, 3206, 3297, 3208).</p>
Claim 6	Hager/Lazar
A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less than 250 mTorr, and in the second chamber is less than 0.7 mTorr.	<p>The pressures in Hager's first and second vacuum chambers are above 500 mTorr (2000 mTorr in Hager's first chamber) and 1 mTorr (8 mTorr in Hager's second chamber). However, it would have been obvious to use pumps that would achieve slightly lower pressures in these chambers.</p> <p>The pressure in Lazar's first chamber is below 250 mTorr (1.5×10^{-1} Torr) and the pressure in the second chamber is below 0.7 mTorr (7×10^{-6} Torr). (Fig. 1, 3206, 3207).</p>
Claim 7	Hager/Lazar
A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less than 175 mTorr, and in the second chamber is less than 0.5 mTorr.	<p>The pressures in Hager's first and second vacuum chambers are above 500 mTorr (2000 mTorr in Hager's first chamber) and 1 mTorr (8 mTorr in Hager's second chamber). However, it would have been obvious to use pumps that would achieve slightly lower pressures in these chambers.</p> <p>The pressure in Lazar's first chamber is below 175 mTorr (1.5×10^{-1} Torr) and the pressure in</p>

	the second chamber is below 0.5 mTorr (7×10^{-6} Torr. (Fig. 1, 3206, 3207).
Claim 8	Hager/Lazar
A mass spectrometer as in claim 6 or 7 in which the offset voltage is ± 10 volts.	<p>Hager states that "[c]onventional DC offsets are also applied to the various rods and to the interface plates from the DC power supply 38." (Col. 6:11-12).</p> <p>In Lazar's system, there is an adjustable DC offset voltage between the "interquad lens" (6) and the second quadrupole ion guide. (Fig. 1, 3206, 3297, 3208).</p>

As shown in the charts, Hager discloses each element of claims 4-8 except the inclusion of an ion guide in the first of the two successive vacuum chambers the precede the mass analyzer and the pressure ranges recited in dependent claims 5-7. However, Lazar teaches the benefits of two successive ion guide stages preceding a mass analyzer, and Lazar teaches the pressure ranges recited in claims 5-7. It would have been obvious to a person skilled in the art as of 1999 in view of Lazar's teaching of a double ion guide interface to add a multipole ion guide to the first vacuum chamber of Hager and apply the DC voltage between the entrance orifice (lens) and the ion guide, as in the first ion guide chamber of Lazar. The person skilled in the art would have been motivated to do so and would have expected success based on the well-known advantages of multipole ion guides for containing and transmitting ions through differentially pumped vacuum stages in a multistage interface, as exemplified by Lazar. It would also have been obvious to use pumps in the system of Hager that would achieve slightly lower pressures within the ranges claimed in claims 5-7 in the first and second vacuum chambers.

Therefore claims 4-8 are unpatentable over Hager in view of Lazar under 35 U.S.C. § 103.

Claims 4-8 are also unpatentable over Buchanan in view of either Smith or Thomson for the reasons discussed above with regard to claim 1 on pages 31-32.

4. Claim 9 Is Unpatentable as Anticipated by Hager, or as Obvious Over Lazar in View of Smith, or Buchanan in View of either Smith or Thomson

Claim 9	Hager
The method of analyzing ions in a mass analyzer which includes a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure comprising the steps of:	Hager discloses a method of analyzing ions in a mass analyzer (quadrupole mass analyzer). The system includes a chamber (region 28 pumped by pump 29) at a pressure of 2 torr and a chamber (chamber 30 pumped by pump 31) at lower pressure of 8×10^{-3} torr. Col. 5:53-58.
forming sample ions at atmospheric pressure with some of the sample ions combining with solvent ions to form adduct ions,	Hager states that “[i]ons generated by electrospray ionization techniques may enter the vacuum chamber as monomers, monomers clustered with solvent molecules, and possibly multimers with and without solvent molecules attached.” Col. 10:45-48.
guiding said sample ions and adduct ions through at least a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure,	Hager states that ions are guided through chamber 28 and chamber 30, which contains an RF-only quadrupole ion guide Q0. Col. 5:53-58.
adding translational kinetic energy to said adduct ions as they travel through said chambers such that in the second chamber the adduct ions are dissociated without fragmenting the sample ions prior to entering the mass analyzer.	Hager discloses adding translational kinetic energy to the adduct ions as they travel through the chambers 28 and 30 by applying DC offset voltages between the orifice and skimmer in chamber 28 and between the skimmer and Q0 in chamber 30 such that adduct ions are dissociated in the chamber 30. Hager states: “Various stages of declustering are commonly used to reduce this mixture of ionic species to a larger proportion of bare monomer ions to solvated ions. Conventional declustering methodologies include . . . collisional dissociation by acceleration of the ions through relatively high pressure regimes using voltage gradients between the orifice and skimmer and between the skimmer and Q0.” Col. 10:51-56.

Hager discloses each element of claim 9. The collisional dissociation of adduct ions in chamber 30 occurs as a consequence of the acceleration provided by voltage gradient between the skimmer and Q0. Therefore, claim 9 is unpatentable as anticipated by Hager.

Claim 9 is also unpatentable because its method would have been obvious over Lazar in view of Smith as set forth in the claim charts below:

Claim 9	Lazar/Smith
The method of analyzing ions in a mass analyzer which includes a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure comprising the steps of:	Lazar discloses a method of analyzing ions in a mass analyzer (TOF mass analyzer) in a mass spectrometer system that includes a first chamber maintained at a pressure of 1.5×10^{-1} Torr and a second maintained at a lower pressure of 7×10^{-6} Torr. (3206-07; Fig. 1.)
forming sample ions at atmospheric pressure with some of the sample ions combining with solvent ions to form adduct ions,	Lazar specifically notes the formation of adduct ions: "However, the paraquat spectrum was mainly composed of a series of ion clusters. The signal intensity at 93 <i>m/z</i> was extremely weak and dependent on the first quadrupole offset voltage." (3208.) Sample ions are formed at atmospheric pressure using an ESI source, which, as Smith observes, gives rise to formation of adduct ions: "Residual association of solvent (or other neutral species) at typical ESI source conditions is likely ubiquitous." ⁴ (56.)
guiding said sample ions and adduct ions through at least a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure,	In device disclosed by Lazar , ions are guided through the first and second (lower pressure) chambers by multipole ion guides. (3206; Fig. 1.)
adding translational kinetic energy to said adduct ions as they travel through said chambers such that in the second chamber the adduct ions are dissociated without fragmenting the sample ions prior to entering the mass analyzer.	Lazar discloses that translational kinetic energy is added to any adduct ions as they travel through the chambers by DC offset voltages between the multipole ion guides and their respective preceding lenses: "We also monitored the signal intensity as a function of the voltage applied to each ion optics element. A very strong dependence was found for the skimmer, <i>rods offset</i> , and interquad lens voltage." (3208.) While Lazar does not observe that dissociation of adduct ions occurs in the second chamber,

⁴ See also Cole at 120 ("In any design of an API mass spectrometer, the problem of the formation of cluster ions is addressed. Polar molecules that tend to cluster with ions are water and solvent vapor present in air or generated by the evaporation of the elute . . .").

	<p>Smith describes dissociation of adduct ions without fragmenting sample ions by application of a DC offset voltage between an orifice and an ion guide in the range of 5-40 V in a pressure environment similar to that in the second ion guide chamber of Lazar. (Smith at 56, 1st col.) The pressure of Smith's chamber is of "the order of 10^{-6} to 10^{-5} torr" and the pressure of Lazar's second ion guide chamber is 7×10^{-6} torr. (Smith at 54, 2nd col.; Lazar at 3207.)</p>
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The charts above show that Lazar discloses each of the elements of claim 9, except that Lazar does not state that adding translational kinetic energy to adduct ions as they travel through the chambers such that in his second chamber, the DC offset is adjusted specifically to convert solvent adduct ions to sample ions in his second ion guide chamber. It was well-known to those skilled in the art to dissociate adduct ions without dissociating sample ions in ion guide chambers at various pressures by adjusting the DC offset voltage appropriately. It would have been obvious in view of Smith to adjust the DC offset voltage of Lazar's second ion guide appropriately to convert adduct ions where present to sample ions at the similar pressure of Lazar's second ion guide chamber without fragmentation of the sample ions. The person of ordinary skill in the art as of 1999 would have been motivated to do so and would have expected success on the basis of his understanding of the collisional dissociation technique for converting adduct ions to sample ions and the well-known implementation of the technique using a DC offset voltage between a multipole ion guide and a preceding lens. Therefore, claim 9 is unpatentable over Lazar in view of Smith under 35 U.S.C. § 103.

Claim 9 is also unpatentable over Buchanan in view of either Smith or Thomson for the reasons discussed above with regard to claim 1 on pages 31-32.

III. CONCLUSION

Substantial new questions of patentability are introduced by the cited references, as indicated in the claim charts and analysis set forth above. Based on the foregoing, reexamination is requested.

Respectfully submitted,

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